a7 cont.

46. The dietary supplement of claim 38, wherein said at least one enzyme comprises about 24% or less of said dietary supplement by weight.

47. The dietary supplement of claim 38, wherein said dietary supplement is PROVEX*CV*™ or PROVEX*CV*2™.--

REMARKS

The specification has been amended to include a statement of priority and to insert proper trademark designations. No new matter has been added by these amendments.

The Examiner rejected claims 1-31 and withdrew claims 32-37 from consideration. Claims 1-3, 6-9, 12-14, 22-25, 29, and 30 have been amended herein, and claims 32-37 have been cancelled without prejudice. In addition, claims 38-47 have been added herein. Thus, claims 1-31 and 38-47 are pending. The application as originally filed supports these claim amendments and these new claims. Thus, no new matter has been added. In light of these amendments and following remarks, Applicant respectfully requests reconsideration and allowance of claims 1-31 and 38-47.

Rejections under 35 U.S.C. §112, second paragraph

The Examiner rejected claims 1-14 and 22-31 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that claims 1-14 and 22-31 are unclear with respect to the term "flavonoid source." Applicant respectfully submits that claims 1, 2, 6-9, 22, 23, 25, 29, and 30 have been amended herein to recite an extract as opposed to a flavonoid source. In light of these amendments, Applicant respectfully requests withdrawal of the rejection of claims 1-14 and 22-31 under 35 U.S.C. §112, second paragraph.

The Examiner also rejected claim 19 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that claim 19 is unclear with respect to the term "phytosome." Applicant respectfully submits that a person having

ordinary skill in the art would have understood that the term "phytosome" as used in claim 19 refers to complexes formed between flavonoids and phospholipids. See, e.g., Bombardelli, *Boll. Chim. Farm.*, 130(11):431-8 (1991), a copy of which is attached to the accompanying Information Disclosure Statement. In light of these amendments, Applicant respectfully requests withdrawal of the rejection of claim 19 under 35 U.S.C. §112, second paragraph.

In addition, the Examiner rejected claims 23 and 24 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner stated that claims 23 and 24 broaden rather than limit claim 22. Applicant respectfully submits that claims 23 and 24 both limit claim 22. For example, claim 22 recites a dietary supplement that can contain a single extract or a plurality of extracts. Claim 23, however, recites that the dietary supplement must contain a plurality of extracts. In addition, claim 24 recites that the dietary supplement is PROVEXCV™. In light of the above, Applicant respectfully requests withdrawal of the rejection of claim 23 and 24 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 1-31 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner stated that the claims do not bear a reasonable correlation to the data provided in Applicant's specification and that the state to the art regarding phytomedicine is highly unpredictable. The Examiner also stated that Applicant's specification lacks a working example that would indicate that admixtures of individual constituents of PROVEXCV™ with a digestive enzyme would in fact display similar effects *in vivo*, concluding that "one of ordinary skill in the art would have to rigorously test each constituent claimed individually in order to ascertain the effectiveness of each substance alone." In addition, after questioning the make-up of extracts as well as the methods for making extracts, the Examiner concluded that (1) a person of ordinary skill in that art "could not be entirely sure that a grape skin extract from one company would be exactly the same grape skin extract from another

company," (2) "it would require undue experimentation in order to create a composition which would display parallel results which Applicant's have provided in the disclosure regarding PROVEXCV," and (3) "because of the large number of inoperable embodiments claimed, it would require a substantial inventive contribution of the ordinary artisan to practice the claimed invention."

Applicant respectfully disagrees. Present claims 1-31 recite dietary supplements as well as methods that involve administering dietary supplements. In each case, the recited dietary supplement must contain (1) an enzyme and (2) an extract containing a flavonoid. In addition, each claim recites that the dietary supplement must be effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. Thus, any dietary supplement that contains an enzyme and an extract containing a flavonoid while being ineffective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less is not within the scope of the claims.

Applicant's specification teaches that dietary supplements containing both an enzyme and an extract containing flavonoid can be effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. Moreover, Applicant's specification teaches how to obtain enzymes and extracts, how to mix enzymes and extracts to form dietary supplements effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less, and how to confirm that a particular dietary supplement is effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. For example, Applicant's specification teaches that extracts containing a flavonoid can be obtained from grape seeds, grape skins, ginko biloba, bilberry, and other similar fruits. See, e.g., page 13, lines 11-14 of Applicant's specification. Thus, a person having ordinary skill in the art reading Applicant' specification would have been capable of using standard extraction procedures to obtain an extract from, for example, grape seeds such that the extract contains a flavonoid. Alternatively, as set forth in Applicant's specification, a person of ordinary skill in the art would have been capable of obtaining an extract containing a flavonoid by simply purchasing a grape seed extract, grape skin extract, ginko biloba extract, bilberry extract, or any other similar type of fruit extract

from any company that sells such extracts. See, e.g., page 19, lines 1-26 of Applicant's specification.

Likewise, Applicant's specification teaches that enzymes can be combined with extracts containing a flavonoid to form dietary supplements effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. For example, Applicant's specification teaches that enzymes can be combined with extracts to create a dietary supplement in the form of a 380 mg capsule that is effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. See, e.g., page 17, lines 26-35 of Applicant's specification. Applicant's specification also teaches methods for assessing a dietary supplement's effectiveness for inhibiting platelet activity and LDL cholesterol oxidation in a mammal. For example, Applicant's specification teaches that the Foltz Model or a platelet aggregometry test can be used to assess platelet activity. See, e.g., page 6, line 31 through page 11, line 14 of Applicant's specification. Thus, a person having ordinary skill in that art at the time Applicant filed reading Applicant's specification would have been capable of mixing an enzyme with an extract containing a flavonoid to form a dietary supplement that is effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1-31 under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §102(b)

The Examiner rejected claims 1-5, 9-11, and 22 under 35 U.S.C. §102(b) as being anticipated by Balch *et al.* pages 20-21 and 47-48 (the Balch *et al.* reference). Specifically, the Examiner cited the Balch *et al.* reference stating that compositions "comprising flavanoids and digestive enzymes were known at the time of the Instant application." In addition, the Examiner indicated that the limitation requiring the dietary supplement to be effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less is "merely considered functional intended use language, and holds no patentable weight." The Examiner, however, proceeded to state that (1) a prima facie case of anticipation is established when "the PTO shows a sound basis for believing that the products of the applicant

and the prior art are the same" and (2) the Applicant "has the burden of showing that they are not."

Applicant respectfully disagrees. Present claims 1-5, 9-11, and 22 recite dietary supplements that must contain both an enzyme and an extract containing a flavonoid. In addition, each claim recites that the dietary supplement must be effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. The Balch *et al.* reference does not disclose a dietary supplement that (1) contains both an enzyme and an extract containing a flavonoid and (2) is effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. In fact, at no point does the Balch *et al.* reference disclose an enzyme in combination with an extract containing a flavonoid, let alone a dietary supplement containing this combination such that the dietary supplement is effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. Moreover, the Balch *et al.* reference never mentions an extract containing a flavonoid.

A claim is anticipated only if each and every element as set forth in the claim is found in a single reference. See, e.g., Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d. 628, 631 (Fed. Cir. 1989) and MPEP §2131. Since the Balch *et al.* reference fails to disclose each and every recited claim element, claims 1-5, 9-11, and 22 are not anticipated. In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1-5, 9-11, and 22 under 35 U.S.C. §102(b).

Rejections under 35 U.S.C. §103(a)

The Examiner rejected claims 1-11 and 21-24 under 35 U.S.C. §103(a) as being unpatentable over Gaynor *et al.* (U.S. Patent No. 5,904,924) in view of Balch *et al.* and further in view of Handel *et al.* (U.S. Patent No. 5,387,422). Specifically, the Examiner stated that (1) Gaynor *et al.* "created a composition comprising grape seed extract, grape skin extract, bilberry, and ginkgo biloba extract," (2) Balch *et al.* teach that digestive enzymes such as bromelain aid in digestion, and (3) Handel *et al.* taught "that fungal proteases obtained by Aspergillus were also acid stable." In addition, the Examiner concluded that one of ordinary skill in the art "would have been motivated to combine the composition disclosed by Gaynor et al. with a protease

composition comprising a fungal protease, an acid stable protease and bromelain in order to effectively aid digestion of the composition."

Applicant respectfully disagrees. Proper analysis under §103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition, and (2) whether the prior art would also have revealed that in so making, those of ordinary skill would have had a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Present claims 1-11 and 21-24 recite dietary supplements that (1) contain an enzyme and an extract containing a flavonoid, and (2) are effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. Thus, to be obvious, the prior art must not only suggest to those of ordinary skill in the art that they should make a dietary supplement that (1) contains an enzyme and an extract containing a flavonoid and (2) is effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less, but also must reveal that in so making, those of ordinary skill would have had a reasonable expectation of success in achieving such a dietary supplement.

The Gaynor *et al.* reference discloses a 969 gram mixture of 55 dried ingredients ranging from bee pollen and dandelion to biotin and inositol. The Balch *et al.* reference discloses that quercetin may effectively treat and prevent asthma and should be taken in conjunction with bromelain to enhance absorption. The Handel *et al.* reference discloses using a proteolytic enzyme food supplement containing an acid protease fungal enzyme and a semi-alkaline protease fungal enzyme to convert ingested dietary protein into free amino acids and short chain peptides. At no point does the combination of references suggest combining an enzyme with an extract containing a flavonoid to form a dietary supplement that is effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. In fact, none of the cited references mentions making a dietary supplement effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at any dosage, let alone at a dosage of about 30 mg/Kg or less.

Even assuming, for the sake of argument, that the cited references suggest to those of ordinary skill in the art that they should make the presently claimed dietary supplement, the cited references fail to provided the required reasonable expectation of success in achieving such a

dietary supplement. At no point do the cited references, either alone or in combination, provide any indication that an enzyme can be combined with an extract to form a dietary supplement that is effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. In fact, a person of ordinary skill in the art would have appreciated that the cited references provide no information about combining enzymes with extracts to form dietary supplements effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at any dosage.

Taken together, the cited references (1) fail to suggest to those of ordinary skill that they should make the recited dietary supplements, and (2) fail to reveal that those of ordinary skill would have had a reasonable expectation of success in achieving the recited dietary supplements. Thus, the cited references do not render the present claims obvious.

In light of the above, Applicant respectfully requests withdrawal of the rejections of claims 1-11 and 21-24 under 35 U.S.C. §103(a).

The Examiner also rejected claims 25-31 under 35 U.S.C. §103(a) as being unpatentable over Pace-Asciak *et al.* in view of Balch *et al.* Specifically, the Examiner stated that it "was known at the time of the instant application that grapes (grape seed and grape skin) contained phytochemicals such as quercetin and resveratrol which were shown to decrease platelet aggregation as evidenced by the entirety of the reference disclosed by Pace-Asciak *et al.*" The Examiner then concluded that:

> One of ordinary skill in the art would have had a reasonable expectation that a composition containing extracts from grapes, such as grape seed or grape skin would intrinsically contain phytochemicals such as resveratrol and quercetin which were known to decrease platelet activity in vivo. Thus, it would not have required a substantial inventive contribution to have added other ingredients to an already pharmaceutically effective phytochemicals in order to achieve similar effects. One would have been motivated to have added a digestive enzyme such as bromelain, since, as Balch et al. discussed supra, bromelain and quercetin acted synergistically in providing a more bioavailable quercetin in vivo.

Applicant respectfully disagrees. Again, proper analysis under §103 requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary

skill in the art that they should make the claimed composition, or carry out the claimed process, and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have had a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Present claims 25-31 recite dietary supplements that (1) contain an enzyme and an extract containing a flavonoid, and (2) are effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. Thus, to be obvious, the prior art not only must suggest to those of ordinary skill in the art that they should make a dietary supplement that (1) contains an enzyme and an extract containing a flavonoid and (2) is effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less, but also must reveal that in so making, those of ordinary skill would have had a reasonable expectation of success in achieving such a dietary supplement.

The Pace-Asciak *et al.* reference discloses that pure resveratrol (129.9 μmol/L), pure quercetin (101.7 μmol/L), and dealcoholized red wine (about 220 μmol/L) can inhibit platelet aggregation by 50 percent when added to platelets in a dish. At no point does the Pace-Asciak *et al.* reference, either alone or in combination with the Balch *et al.* reference, suggest combining an enzyme with an extract containing a flavonoid to form a dietary supplement that is effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. In fact, at no point does the combination of the Pace-Asciak *et al.* and Balch *et al.* references teach or suggest combining an enzyme with an extract containing a flavonoid. Again, the Balch *et al.* reference never mentions an extract containing a flavonoid.

Even assuming, for the sake of argument, that the Pace-Asciak *et al.* and Balch *et al.* references suggest to those of ordinary skill in the art that they should make the presently claimed dietary supplement, these cited references fail to provided the required reasonable expectation of success in achieving such a dietary supplement. At no point do the Pace-Asciak *et al.* and Balch *et al.* references, either alone or in combination, provide any indication that an enzyme can be combined with an extract to form a dietary supplement that is effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less. In fact, a person of ordinary skill in the art would have appreciated that the Pace-Asciak *et al.* and Balch *et al.* references provide no information about combining enzymes with

extracts to form dietary supplements effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at any dosage.

Taken together, the Pace-Asciak *et al.* and Balch *et al.* references (1) fail to suggest to those of ordinary skill that they should make the recited dietary supplements, and (2) fail to reveal that those of ordinary skill would have had a reasonable expectation of success in achieving the recited dietary supplements. Thus, the Pace-Asciak *et al.* and Balch *et al.* references do not render the present claims obvious.

In light of the above, Applicant respectfully requests withdrawal of the rejections of claims 25-31 under 35 U.S.C. §103(a).

CONCLUSION

Applicant respectfully submits that claims 1-31 and 38-47 are in condition for allowance, which action is requested. Enclosed is a check for excess claim fees and the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: April 27, 2001

J. Patrick Finn III, Ph.D.
Reg. No. 44,109

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

Version with markings to show changes made

In the claims:

Claims 1-3, 6-9, 12-14, 22-25, 29, and 30 have been amended as follows:

1. (Amended Once) A dietary supplement comprising at least one [flavonoid source] extract and [an] at least one enzyme, wherein said at least one extract comprises a flavonoid, said supplement effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less.

2. (Amended Once) The supplement of claim 1, wherein said [flavonoid source] at least one extract comprises [one or more of] a grape seed extract, grape skin extract, bilberry extract, or ginkgo biloba extract [or quercetin].

3. (Amended Once) The supplement of claim 1, wherein said at least one enzyme comprises [one or more of] a fungal protease, acid stable protease, or bromelain.

6. (Amended Once) The supplement of claim 1, wherein said [flavonoid source] at least one extract comprises [at least one] a grape extract.

7. (Amended Once) The supplement of claim 1, wherein said [flavonoid source] at least one extract comprises a bilberry extract.

8. (Amended Once) The supplement of claim 1, wherein said [flavonoid source] at least one extract comprises a ginkgo biloba extract.

9. (Amended Once) The supplement of claim 1, wherein said [flavonoid source] supplement comprises quercetin.

12. (Amended Once) The supplement of claim 1, wherein said at least one enzyme comprises about 24% or less of said supplement by weight.

13. (Amended Once) The supplement of claim 1, wherein said dietary supplement [comprises] is PROVEX*CV*™.

14. (Amended Once) The supplement of claim 1, wherein said dietary supplement [comprises] is PROVEX*CV*2™.

22. (Amended Once) A dietary supplement comprising an unfermented [flavonoid source] extract and an enzyme, wherein said extract comprises a flavonoid, said supplement effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less.

23. (Amended Once) The supplement of claim 22, wherein said supplement comprises a plurality of [flavonoid sources] extracts, wherein each of said plurality of extracts comprises a flavonoid.

24. (Amended Once) The supplement of claim 23, wherein said supplement [comprises] is PROVEX*CV*2™.

25. (Amended Once) A method to inhibit platelet activity or LDL cholesterol oxidation in a mammal, said method comprising administering a dietary supplement comprising at least one [flavonoid source] extract and [an] at least one enzyme to said mammal, wherein said at least one extract comprises a flavonoid, said supplement effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less.

29. (Amended Once) A method to treat a condition associated with platelet activity or LDL cholesterol oxidation, said method comprising administering a dietary supplement comprising at least one [flavonoid source] extract and [an] at least one enzyme to said mammal, wherein said at

least one extract comprises a flavonoid, said supplement effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less.

30. (Amended Once) An article of manufacture comprising a dietary supplement [comprising] and packaging material, wherein said dietary supplement comprises at least one [flavonoid source] extract and [an] at least one enzyme, wherein said extract comprises a flavonoid, said supplement effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less [contained within a packaging material], and wherein said packaging material is labeled to indicate that said dietary supplement is useful for reducing platelet activity or LDL cholesterol oxidation or both.

Claims 38-47 have been added as follows:

--38. A dietary supplement comprising at least two flavonoids and at least one enzyme, said supplement effective for inhibiting platelet activity and LDL cholesterol oxidation in a mammal at a dosage of about 30 mg/Kg or less.

39. The dietary supplement of claim 38, wherein said at least two flavonoids are selected from the group consisting of catechins, procyanidins, proanthocyanidins, quercetin, and rutin.

40. The dietary supplement of claim 38, wherein said at least one enzyme is selected from the group consisting of fungal proteases, acid stable proteases, and bromelain.

41. The dietary supplement of claim 38, wherein said dietary supplement comprises a grape seed extract, grape skin extract, bilberry extract, or ginkgo biloba extract.

42. The dietary supplement of claim 38, wherein said dietary supplement is effective for inhibiting platelet activity and LDL cholesterol oxidation at a dosage of about 20 mg/Kg or less.

43. The dietary supplement of claim 38, wherein said dietary supplement is effective for inhibiting platelet activity and LDL cholesterol oxidation at a dosage of about 10 mg/Kg or less.

44. The dietary supplement of claim 38, wherein said dietary supplement is effective for inhibiting blood platelet activity for at least four hours following ingestion of said dietary supplement.

45. The dietary supplement of claim 38, wherein said dietary supplement is effective for inhibiting platelet activity in a mammal at a dosage of about 30 mg/Kg or less and following administration of epinephrine at a dosage of about 0.2 μg/Kg/min.

46. The dietary supplement of claim 38, wherein said at least one enzyme comprises about 24% or less of said dietary supplement by weight.

47. The dietary supplement of claim 38, wherein said dietary supplement is PROVEX*CV*™ or PROVEX*CV*2™.--